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THE FORMATION OF CONGLUTINATION THROMBI IN THE LIVER OF DOGS AFTER INJECTIONS OF WITTE'S PEPTONE

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In the course of studies on the ereptase content of the blood and organs of dogs, an attempt was made to increase the amount of this ferment by repeated injections of Witte's peptone. The injections were given into the saphenous vein at intervals of 2-4 days. A first dose of 1 gm. for an average sized dog was used. The succeeding doses were increased until several animals received 10 gm. of peptone intravenously at one time. The injections were made fairly slowly. The reaction following the first dose was quite marked—discharge of feces and urine, sometimes vomiting, and marked depression, but no definite evidence of the pronounced bronchoconstriction as observed by Hirschfelder[1] in guinea-pigs which had been injected with peptone. The reactions from the subsequent larger doses were either absent or less severe. The animals were killed by chloroforming immediately after the last injection or at the end of 8 and 15 days. For purposes of comparison a number of dogs that died as a result of acute peptone shock following a first injection are included in this series.

The liver in all the animals showed characteristic microscopic changes. In the dogs dying in acute peptone shock the changes closely resemble the condition seen in marked passive hyperemia. There is an excess of blood in the central veins and sinusoids and in the branches of the portal vein in Glisson's capsule. The sublobular and other branches of the hepatic vein are not distended. In many places the sinusoids show unusually wide, localized, circular or oval dilatations.

In the livers of dogs killed after 8 and 15 days, respectively, solid plugs are seen occupying round or oval spaces where the sinusoids are distended to 2-4 times their normal width. The number of these plugs does not differ greatly in different livers, and range from 1-6 in a single (low power) field of the microscope. They occur in all parts of the lobule but are most numerous in the midzonal and peripheral portions. They are not found in the branches of the portal vein. The hepatic cells adjacent to the plugs appear normal. No other organs show such masses in any of their blood vessels.

These intrasinusoidal plugs are composed of material that is partly granular and partly homogeneous or hyaline, and most of them contain granules of reddish brown pigment. They take the eosin stain. Stains for fibrin show

Received for publication Nov. 11, 1918.

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[1] Jour. Exper. Med., 1910, 12, p. 586.

that this is present in small amount in the 8-day specimens. The plugs in some instances do not fill the spaces in which they lie. In the 15-day specimens, and to a less extent in the 8-day specimens, these masses have been invaded by large mononuclear or transitional ("endothelial") leukocytes, many of which contain granules of pigment. No genetic relation can be established between these cells and the adjacent sinusoidal endothelium which appears normal. This may be due to the late stage at which the specimens were observed (8-15 days).

In attempting to explain the origin of these intrasinusoidal plugs, two possibilities suggest themselves. In the first place, they may be due to a localized thrombosis of the sinusoids, such as is not infrequently seen in cases of passive hyperemia of the liver. Nolf[2] has shown that if a solution of peptone is injected slowly, the coagulability of the blood is greatly increased. He has employed repeated injections of peptone to prevent hemorrhage in typhoid fever, and in the treatment of hemophilia and related conditions. Pozerski and Pozerska[3] found that the so-called immunity to the anticoagulant action of peptone after injections is more lasting than the resistance to its depressor action. Nolf[4] has explained the occurrence of leukopenia after injections of peptone on the basis of damage to the endothelium of the hepatic capillaries thus rendering them more sticky for leukocytes. There is a possibility, therefore, that the coagulability of the blood of the animals in these experiments was increased by the injections of the peptone. Unfortunately no studies were made to clear up this point at the time, because the primary object of the experiments was a study of ferments and the changes in the liver were only discovered during the routine microscopic examination of the tissues of animals used in experiments in this laboratory.

If such increased coagulability did exist, thrombosis in the intralobular capillaries of the liver would be most likely to occur in the locations in which these plugs have been found, namely, in the circular or oval dilatations of the sinusoids where the blood flow would be slowest and any damage to the endothelium probably the greatest.

On the other hand, the formation of plugs from conglutinated red blood corpuscles must be considered. Such thrombi have been observed by Flexner[5] after the injection of certain toxalbumins, such as abrin and ricin, and by Pearce[6] and by Karsner and Aub[7] after injections of hemagglutinating serum. The masses of agglutinated erythrocytes produced by the toxalbumin and by the serum were formed in the circulating blood and carried to the liver. Here they lodged as a rule in the mid-zonal region of the lobule, which, as pointed out by Opie,[8] is the location at which minute emboli in the portal vein usually come to rest. Pearce also observed similar masses in the vessels of the kidneys of animals injected with hemagglutinative serums.

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[2] Compt. rend. Soc. de biol., 1916, 79, p. 648.
[3] Ann. de l'Inst. Pasteur, 1913, 27, p. 120.
[4] Arch. Internat. de Physiol., 1904, 1, p. 242.
[5] Jour. Med. Research, 1902, 8, p. 316.
[6] Jour. Med. Research, 1904, 12, p. 329.
[7] Jour. Med. Research, 1913, 28, p. 377.

In the condition here described, the mechanism of conglutination of the red blood cells was probably somewhat different. There is no evidence that Witte's peptone causes agglutination of the red cells of the dog as do abrin and ricin. After injections of peptone there is an obstruction to the outflow of blood from the liver. The central veins, sinusoids and distributing branches of the portal vein are distended with blood. At the same time there is a marked loss of fluid from the blood in the liver as shown by numerous experiments on lymph formation by Heidenhain,[9] Starling,[10] Yanagawa[11] and others.

The stagnation of blood in the dilated sinusoids, with the escape of much of its fluid into the lymph stream, leads to the formation of densely packed aggregations of red blood corpuscles. This occurs most readily in the circular or oval dilatations previously mentioned. Such groups of corpuscles, closely crowded together with very little intervening fluid, do not readily break up when the obstruction to outflow is relieved and the circulation in the liver restored to normal. Instead, they become fused into solid masses in which the individual corpuscles lose their identity.

The hepatic epithelium adjacent to the intrasinusoidal plugs shows no definite evidence of either hyaline necrosis as observed by Pearce[6] and by Karsner and Aub[7] after injections of hemagglutinating serum, or of the granular necrosis noted by Mallory[12] after injections of lycopodium spores into the portal vein. It cannot now be stated whether the absence of such necrosis following the injections of peptone here described is due to the late stage at which the examinations were made, complete regeneration having taken place in the meantime; or to differences in the extent of the occlusion of the sinusoids; or to the absence of cytotoxic amboceptor from the conglutinated corpuscles, which Pearce[6] and Karsner and Aub[7] believed was liberated from the thrombi produced as a result of the injection of hemagglutinating serums.

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[8] Jour. Med. Research, 1904, 12, p. 147.
[9] Arch. ges. Physiol., 1891, 49, p. 209.
[10] Jour. Physiol., 1894, 16, p. 224.
[11] Jour. Pharm. and Exper. Therap., 1917, 9, p. 75.
[12] Jour. Med. Research, 1901, 6, p. 264.

SUMMARY

In dogs dead of acute peptone shock, the microscopic appearance of the liver resembles very closely that of marked passive hyperemia.

In the liver of dogs which have received repeated injections of Witte's peptone intravenously, there are found quite constantly in many of the sinusoids solid plugs of more or less homogeneous material.

In the stages of the process here studied (8 and 15 days after the last injection of the peptone), no changes were observed in the adjacent liver cells or endothelium.

It seems probable that these intrasinusoidal masses were formed *in situ* from agglutination of red blood corpuscles in localized areas of unresolved stasis due to obstruction to the outflow of blood from the liver and to the great loss of fluid from the blood in the liver in peptone poisoning.